

WHAT IS CLAIMED IS:

1. A method of screening for modulating agents of a Homer signaling pathway comprising:
 - i) contacting at least one protein or peptide having a proline-type Homer ligand consensus sequence in the presence of a peptidylproline cis-trans isomerase (PPIase) inhibitor with at least one test agent for a sufficient time to allow the components to interact;
 - ii) contacting the protein or peptide of step (i) with a Homer protein;
 - iii) determining whether binding between the at least one protein or peptide and Homer protein is increased or decreased.
2. The method of claim 1, wherein increased or decreased binding between the at least one protein or peptide and Homer protein is indicative of the presence of a modulating agent for a Homer signaling pathway.
3. The method of claim 1, wherein as the concentration of the at least one agent increases, decreased binding of Homer protein to the at least one protein or peptide is indicative of the presence of a competitive Homer ligand.
4. The method of claim 1, wherein the determining step further comprises immunoprecipitation of a complex between the Homer protein and the at least one protein or peptide.
5. The method of claim 1, wherein the PPIase inhibitor shows a biphasic affect at separate concentrations.
6. The method of claim 5, further wherein the PPIase inhibitor is present in at least two concentrations, wherein at least one concentration of the inhibitor does not inhibit Homer binding to the at least one protein or peptide.

7. The method of claim 6, wherein the modulation of Homer protein binding by the agent at the concentration of PPIase inhibitor which does not inhibit binding of the Homer protein is indicative of the presence of an modulating agent of a Homer signaling pathway.
8. The method of claim 1, wherein the PPIase inhibitor is a rotamase inhibitor.
9. The method of claim 1, wherein the PPIase inhibitor is selected from the group consisting of FK506, cyclosporin A, and GPI-1046.
10. The method of claim 7, wherein the PPIase inhibitor is GPI-1046.
11. The method of claim 1, further comprising determining an endpoint assay selected from the group consisting of modulation of Ca^{+2} signaling, modulation of PLC, modulation of Trp channels, modulation of MAP kinase, modulation of PI3kinase, modulation of ion channels, modulation of IP3 channels, modulation of RYR channels, and modulation of growth factor dependent responses.
12. The method of claim 1, wherein the at least one protein or peptide and Homer protein are comprised in a cell or cell lysate.
13. The method of claim 12, wherein the at least one protein or peptide and Homer proteins are comprised in a cell.
14. The method of claim 13, wherein the cell is a transformed cell.
15. The method of claim 14, wherein the at least one amino acid or the Homer protein is recombinant.

16. The method of claim 15, wherein the recombinant at least one protein or peptide is encoded by a nucleic acid encoding a consensus protein or peptide as set forth in accession numbers NP005451, NP037434, AAB97097, NP004548, Q00900, NP003249, NP840084, P009086, Q9JLU4, NP113939, NP067708, Q9WV48, P97836, AAF61375, AAD29417, P000531, AAC50926, P10275, NP776901, NP003295, NP057263, NP000829 or BAA05891.

17. The method of claim 16, wherein the nucleic acid encodes a sequence as set forth in accession number NP005451.

18. The method of claim 1, wherein the Homer ligand consensus sequence is a proline-type 1 Homer ligand consensus sequence or a proline-type 2 Homer ligand consensus sequence.

19. The method of claim 18, wherein the proline-type Homer ligand consensus sequence is set forth in SEQ ID NO: 4.

20. The method of claim 1, wherein the at least one protein or peptide is a synthetic oligopeptide comprising at least 4 amino acid residues, but not more than 10 amino acid residues, having a consensus sequence as set forth in SEQ ID NO: 4.

21. The method of claim 20, wherein the synthetic oligopeptide consists of the protein or peptide as set forth in SEQ ID NO:5.

22. The method of claim 1, wherein the at least one protein or peptide is selected from a protein in the group consisting of synphilin, EF2kinase, p70, Notch 4, AGIE-BP1, cytosolic thymidine kinase, neuronal PAS domain protein 2, zona pellucida sperm binding protein 3 precursor, Shank family of proteins, ryanodine receptor (RYR), p82, androgen receptor, TrpC1, mGluR1a and mGluR5.

23. The method of claim 1, further comprising contacting the protein or peptide of step (i) with at least one PPIase.
24. The method of claim 23, wherein the PPIase is selected from the group consisting of FKBP family, cyclophilin family, and Pin family of PPIases.
25. The method of claim 25, wherein the PPIase is FKBP 52 or FKBP 12.
26. The method of claim 26, wherein the PPIase is FKBP52.
27. The method of claim 1, wherein the Homer protein is human.
28. The method of claim 1, wherein the Homer protein as set forth in the accession numbers selected from the group of consisting of NP 004829, NP 004830, NP 004263, NP 671705, NP 445762, and NP 445761.
29. The method of claim 1, wherein the Homer protein comprises point mutations.
30. The method of claim 29, wherein the Homer protein is as set forth in SEQ ID NO: 7.
31. The method of claim 1, wherein the modulating agent functions as a neuroprotective agent.
32. The method of claim 31, wherein the agent is effective for treating neurodisorders selected from the group consisting of peripheral neuropathies and neurological pathologies related to neurodegeneration.
33. The method of claim 1, wherein the modulating agent functions as an immunosuppressive agent.

34. The method of claim 33, wherein the agent is effective for treating a disorder selected from the group consisting of psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, dermatitis, meningitis, encephalitis, eczema, asthma, skin hypersensitivity reactions, atherosclerosis, leukocyte adhesion deficiency, rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetes mellitus, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, experimental autoimmune encephalomyelitis, Sjorgen's syndrome, juvenile onset diabetes, tuberculosis, sarcoidosis, polymyositis, granulomatosis, vasculitis, pernicious anemia, diseases involving leukocyte diapedesis, CNS inflammatory disorder, multiple organ injury syndrome secondary to septicemia or trauma, autoimmune hemolytic anemia, myasthenia gravis, antigen-antibody complex mediated diseases, and transplantations, including graft vs. host or host vs. graft disease.

35. A method of preserving nerve bundles after surgery by administering to a subject in need thereof a therapeutic amount of a pharmaceutical composition comprising an agent identified by the method of claim 1.

36. A method of modulating sensory perception by administering to a subject in need thereof a therapeutic amount of a pharmaceutical composition comprising an agent identified by the method of claim 1.

37. The method of claim 36, wherein the sensory perception is tactile or temperature perception.

38. The method of claim 35, wherein the agent is administered during or subsequent to a surgical procedure.

39. The method of claim 38, wherein the surgical procedure involves neurological injury from trauma or stroke.

40. The method of claim 38, wherein the surgical procedure is selected from the group consisting of radical prostatectomy and organ transplantation.

41. A method of treating a neurological disorder by administering to a subject in need thereof a therapeutic amount of a pharmaceutical composition comprising an agent identified by the method of claim 1.
42. The method of claim 41, wherein the neurological disorder is selected from the group consisting of peripheral neuropathies and neurological pathologies related to neurodegeneration.
43. The method of claim 42, wherein the neurological disorder is Alzheimer's disease.
44. The method of claim 42, wherein the neurological disorder is Parkinson's disease.
45. The method of claim 42, wherein the neurological disorder is amyotrophic lateral sclerosis.
46. A method of inducing immunosuppression or treating inflammation by administering to a subject in need thereof a therapeutic amount of a pharmaceutical composition comprising an agent identified by the method of claim 1.
47. The method of claim 46, wherein the inducing immunosuppression is effective for treating a disorder selected from the group consisting of psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, dermatitis, meningitis, encephalitis, eczema, asthma, skin hypersensitivity reactions, atherosclerosis, leukocyte adhesion deficiency, rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetes mellitus, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, experimental autoimmune encephalomyelitis, Sjorgen's syndrome, juvenile onset diabetes, tuberculosis, sarcoidosis, polymyositis, granulomatosis, vasculitis, pernicious anemia, diseases involving leukocyte diapedesis, CNS inflammatory disorder, multiple organ injury syndrome secondary to septicemia or trauma, autoimmune hemolytic anemia, myasthenia gravis, antigen-antibody

complex mediated diseases, and transplantations, including graft vs. host or host vs. graft disease.

48. A method of treating hematological disorders by administering to a subject in need thereof a therapeutic amount of a pharmaceutical composition comprising an agent identified by the method of claim 1.

49. The method of claim 48, wherein the hematological disorder is selected from the group consisting of lymphoblastic leukemia, acute or chronic myelogenous leukemia, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, myelodysplastic syndrome, multiple myeloma, and chronic lymphocytic leukemia.

50. A method of diagnosing a Homer signaling disorder comprising:

- (i) isolating a biological sample from a subject;
- (ii) lysing the sample of step (i) in the presence of a PPIase inhibitor;
- (iii) contacting the lysed sample of step (ii) with at least one protein or peptide having a proline-type Homer ligand consensus sequence;
- (iv) contacting the protein or peptide containing sample of step (iii) with a Homer protein; and
- (v) determining whether the at least one consensus containing protein or peptide and Homer protein bind.

51. The method of claim 50, wherein decreased binding between the consensus containing protein and the Homer protein is indicative of a Homer signaling disorder.

52. The method of claim 50, wherein the disorder is associated with increased PPIase activity.

53. The method of claim 50, wherein the disorder is an immunosuppressive disorder, a hematological disorder or a neurological disorder.

54. The method of claim 53, wherein the disorder is an immunosuppressive disorder.
55. The method of claim 54, wherein the immunosuppressive disorder is selected from the group consisting of psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, dermatitis, meningitis, encephalitis, eczema, asthma, skin hypersensitivity reactions, atherosclerosis, leukocyte adhesion deficiency, rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetes mellitus, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, experimental autoimmune encephalomyelitis, Sjorgen's syndrome, juvenile onset diabetes, tuberculosis, sarcoidosis, polymyositis, granulomatosis, vasculitis, pernicious anemia, diseases involving leukocyte diapedesis, CNS inflammatory disorder, multiple organ injury syndrome secondary to septicemia or trauma, autoimmune hemolytic anemia, myasthenia gravis, antigen-antibody complex mediated diseases, and transplantations, including graft vs. host or host vs. graft disease.
56. The method of claim 53, wherein the disorder is a hematological disorder.
57. The method of claim 56, wherein the hematological disorder is selected from the group consisting of lymphoblastic leukemia, acute or chronic myelogenous leukemia, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, myelodysplastic syndrome, multiple myeloma, and chronic lymphocytic leukemia.
58. The method of claim 53, wherein the disorder is a neurological disorder.
59. The method of claim 58, wherein the neurological disorder is selected from the group consisting of peripheral neuropathies and neurological pathologies related to neurodegeneration.
60. The method of claim 51, wherein the PPIase is selected from the group consisting of FKBP family, cyclosporin family and the Pin family of PPIases.

61. The method of claim 50, wherein the PPIase inhibitor is selected from the group consisting of FK506, cyclosporin A, and GPI-1046.

62. The method of claim 50, wherein the concentration of the PPIase inhibitor does not inhibit the binding between the consensus containing protein or peptide to the Homer protein.

63. The method of claim 62, wherein the contacting time for the inhibitor containing lysate is not sufficient to inhibit the binding between the consensus containing protein or peptide to the Homer protein at that concentration of inhibitor.

64. The method of claim 50, wherein the Homer ligand consensus sequence is proline-type 1 Homer ligand consensus sequence or a proline-type 2 ligand consensus sequence.

65. The method of claim 50, wherein the protein is selected from the group consisting of synphilin, EF2kinase, p70, Notch 4, AGIE-BP1, cytosolic thymidine kinase, neuronal PAS domain protein 2, zona pellucida sperm binding protein 3 precursor, Shank family of proteins, ryanodine receptor (RYR), p82, androgen receptor, TrpC1, mGluR1a and mGluR5.

66. A method of determining the efficacy of a PPIase inhibitor comprising:

- (i) isolating a biological sample from a subject before and after administering a PPIase inhibitor;
- (ii) lysing the sample of step (i);
- (iii) contacting the lysed sample of step (ii) with at least one protein or peptide having a proline-type Homer ligand consensus sequence;
- (iv) contacting the protein or peptide containing sample of step (iii) with a Homer protein; and
- (v) determining whether the at least one consensus containing protein or peptide and Homer protein bind.

67. The method of claim 66, wherein the inhibitor demonstrates a biphasic effect on Homer binding to the at least one protein or peptide as a function of concentration.

68. The method of claim 67, wherein increased or decreased binding between the consensus containing protein and the Homer protein correlates with the therapeutic efficacy of the inhibitor.

69. The method of claim 66, wherein the inhibitor demonstrates a biphasic effect on Homer binding to the at least one protein or peptide as a function of time.

70. The method of claim 69, wherein increased or decreased binding between the consensus containing protein and the Homer protein correlates with the therapeutic efficacy of the inhibitor.

71. The method of claim 66, wherein the inhibitor is being administered to treat an immunological disorder, a neurological disorder or a hematological disorder.